

Two phenotypes of depression in epilepsy: Improving its diagnosis in clinical practice

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Abstract

We use data-driven profiling to determine if there are distinctive phenotypes of depression in epilepsy. Psychiatric and neuropsychological functioning of 91 patients with focal epilepsy is compared to that of 77 controls (N=168). Cluster analysis of current depressive symptoms identifies three clusters: one comprising non-depressed patients, as well as two phenotypes of depression. The 'Cognitive' phenotype (base-rate=17%) is characterized by self-critical cognitions and dysphoria, with pervasive memory deficits. The 'Somatic' phenotype (7%) is characterized by vegetative depressive symptoms and anhedonia, as well as greater anxiety. Awareness of the features facilitates improved diagnosis of depression in epilepsy and thereby timely treatment. (*100 words*)

Introduction

Depressed mood is the most prominent psychiatric feature of epilepsy. {1}, with patients 43% more likely to develop depression than controls (for a recent systematic review see Rayner and Wilson). {2} Despite the high rate of depression in epilepsy recognized in clinical research studies, in the busy outpatient clinic it goes largely undiagnosed and is frequently not treated. {3,4} The stakes surrounding depression in epilepsy, however, are high. Not only does it diminish quality of life more so than seizure-related factors,[5-7] but suicide is three times more frequent in individuals with epilepsy relative to demographically-matched controls. {8}

Poor recognition of depression in the clinic has been attributed to the observation that the presentation of depression in epilepsy is neither homogenous nor well-captured by formal diagnostic criteria. {9} This study employs data-driven methods to delineate symptom-based phenotypes of depression in people with focal epilepsy, together with their cognitive, clinical, and psychosocial features. Given the numerous links between mood and memory in the primary depression literature and the high prevalence of memory disorders in people with epilepsy, {10,11} we hypothesized that a predominant phenotype of depression in epilepsy would be characterized by cognitive symptoms and prominent psychometric impairments.

Methods and Materials

Participants

The patient cohort (n=91) was recruited while undergoing inpatient characterization of focal seizures in the Comprehensive Epilepsy Programme of Austin Health, Melbourne, between 2010-2015. {12} Of the 91 patients, 76% were diagnosed as having seizures arising from the temporal lobe (46% left hemisphere, 60% lesion positive), and 24% from extratemporal

regions (32% left hemisphere, 73% lesion positive). Epileptological and demographic features of the patients are summarized in Table 1.

[Table 1 about here]

A group of 77 healthy individuals with no neurological or psychiatric history was recruited from the patients' families and broader community to provide a sociodemographically-matched control sample (N=168). Patients and controls were tested separately and asked not to discuss their participation in order to avoid cross-contamination. Participants with epilepsy did not differ from controls in sex, age, or years of education ($P > 0.050$; see Table 1). Controls had a slightly higher mean Full-Scale IQ (FSIQ) than the patients [$t_{(151)} = 2.516$, $P = 0.013$, $\eta^2 = 0.040$, small effect size], however mean scores for both groups fell within the "Average" range (i.e., 90-110). Inclusion criteria for all participants were: (1) aged 18-70, (2) FSIQ ≥ 70 , (3) neurosurgically-naïve, (4) functional English. Patients with a comorbid psychiatric diagnosis other than affective disorder were excluded. The study had approval from the relevant Human Research Ethics Committees and all participants provided written, informed consent.

Materials

Neuropsychiatric Evaluation

In-depth neuropsychiatric evaluation of the patient sample was undertaken using the *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)*, the gold standard measure for diagnosing current and past mood disturbance according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV).^{13} Of particular value, the SCID includes close questioning around atypical symptoms of depression and allows for the diagnosis of minor and unorthodox manifestations of the disorder that some researchers in the field consider to be of especial interest to epilepsy.

Moreover, patients were carefully questioned about depressive symptoms to ensure they could not be attributed to changes in antiepileptic medication.

The *Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)* {14} was administered as a linear self-report measure of current depressive symptoms. Its six items canvass symptoms that do not overlap with commonly comorbid cognitive deficits in epilepsy or the adverse effects of antiepileptic drugs, with each item endorsed on a scale of 1=never to 4=always/often. The minimum score is six (no symptoms), and the maximum 28. NDDI-E scores >15 have been shown to have 90% specificity, 81% sensitivity, and a positive predictive value of 0.62 for a diagnosis of major depression.

The *Patient Health Questionnaire-Generalized Anxiety Disorder-7-item (PHQ-GAD-7)* was developed to assess the severity of current anxiety symptoms in medical populations. {15} Participants assign scores of 0-3 to the response categories of ‘not at all’, ‘several days’, ‘more than half the days’, and ‘nearly every day’, respectively. PHQ-GAD-7 total scores for the seven items range from 0-21; scores of 5, 10, and 15 represent cut-offs for mild, moderate, and severe anxiety, respectively.

Psychosocial function and health-related quality of life

The *Epilepsy Surgery Inventory, 55-item (ESI-55)* {16} was employed as a measure of health-related quality of life in the patient group. It is reliable and valid, and has been used widely in this population.

The *Family Adaptability and Cohesion Scale (FACES-IV)* {17} is a self-assessment of family functioning. It comprises 84 items across six scales, including two that measure healthy dynamics, and four ‘unbalanced’ scales designed to tap low and high cohesion (disengaged and enmeshed) and flexibility (rigid and chaotic). Participants respond on a six-point Likert scale.

Formal Neuropsychological Assessment

The semi-structured *Autobiographical Memory Interview (AMI)* {18} was used to assess personal memories from childhood, early adulthood, and recent life. The *Personal Semantic Schedule* requires participants to recall personally relevant facts (e.g., former addresses); each of the three time-points are scored out of 21 (maximum=63), with a score of ≤ 47 associated with an amnesic syndrome and scores of 48-49 indicative of a probable amnesic syndrome. The *Autobiographical Incident Schedule* asks participants to recall three episodes from each time period (e.g., a wedding). Episodic memories are scored from 0 to 3 (maximum=27) based on their richness in detail and how precisely the incident is located in place and time, with a total score of ≤ 12 associated with an amnesic syndrome, and scores of 13-15 indicative of a probable amnesic syndrome. Inter-rater reliability lies between $r = 0.83-0.86$, with good sensitivity to organic disease.

Neuropsychological evaluation of broader memory functioning was assessed using the *Wechsler Memory Scale-fourth edition (WMS-IV)*. {19} Specifically, auditory-verbal memory was assessed with immediate and delayed recall indices of the Verbal Paired Associates subtest, and visual learning was assessed using the immediate and delayed recall indices of the Design Memory subtest. All subtests were scored according to age-scaled normative data ($M=10$; $SD=3$), with scaled scores ≤ 8 considered indicative of impairment.

Statistical analyses

Analyses were performed using IBM SPSS Statistics (version 22.0), with statistical significance set at $P < 0.050$ (two-tailed). Where data did not meet assumptions for parametric analyses, more conservative alternatives were employed. Given the difference in FSIQ between patients and controls, scatterplots and Pearson Product-Moment correlations were

used to assess the relationships between memory indices and FSIQ. No significant relationships were identified, negating the need to covary for FSIQ in subsequent analyses.

Initial comparison of the demographic, neuropsychological, and psychiatric functioning of the patient cohort with controls was undertaken using Chi-squared analyses with Fisher's Exact Test for categorical variables, independent sample t-tests for continuous variables, and one-sample t-tests for comparing patient performances on WMS-IV to normative data.

To identify phenotypes of depression in epilepsy, cluster analysis was used to classify patients into groups with shared symptom profiles. Cluster analyses is standard methodology for clinical phenotyping as opposed to (for example) factor analysis, which is more strictly suitable in describing the latent structure of a behavioral measure. {20} The nine binary items describing DSM-IV depressive symptoms on the SCID were selected as the indicator variables, within the "10 cases for every variable" criteria recommended for cluster analysis. {20} Hierarchical cluster analysis using Ward's Method was run, with squared Euclidian distances as the similarity measure. Each cluster represents a homogeneous group of patients who share similar responses to the model parameters (i.e., SCID symptoms).

To identify demographic, clinical, psychological, and psychosocial covariates associated with cluster membership we ran bivariate descriptive analyses comparing the depressive phenotypes, or where power was low, inspected frequency trends across groups. For cognitive measures, performances on the AMI and WMS-IV subscales were converted into z-scores relative to normal performances from healthy controls for ease of comparison.

Results

Elevated rates of psychopathology and disturbed cognition in people with epilepsy

Psychiatric evaluation revealed that 39 (43%) epilepsy patients met criteria for a lifetime history of Depressive Disorder and 21 (23%) currently met criteria for a Major Depressive

Episode or Depressive Disorder Not Otherwise Specified. This is appreciably higher than the global point prevalence for primary Depressive Disorder of 4.7% (4.4–5.0%) in the general population. {21} Consistent with this, epilepsy patients endorsed substantially more depressive and anxiety symptoms (NDDI-E: $t_{(151)}=4.487$, $P<0.001$, $d=0.719$, medium-large effect size; PHQ-GAD-7: $t_{(143)}=2.624$, $P=0.010$, $d=0.430$, small-medium effect size; see Figure 1).

Patients also performed worse on all measures of semantic and episodic autobiographic memory (Total, Personal Semantic Schedule: $t_{(147)}=-4.276$, $P<0.001$, $d=0.714$, medium-large effect size; Total, Autobiographical Incident Schedule: $t_{(147)}=-6.276$, $P<0.001$, $d=1.057$, large effect size) as well as auditory-verbal and visual forms of immediate and delayed recall (Verbal Paired Associates-I: $t_{(70)}=-2.541$, $P=0.013$; Verbal Paired Associates-II: $t_{(70)}=-3.625$, $P=0.001$; Design-I: $t_{(72)}=-2.926$, $P=0.005$; Design-II: $t_{(71)}=-3.160$, $P=0.002$).

[Figure 1 goes here]

Two phenotypes of depression in epilepsy

Cluster analysis identified three groups of epilepsy patients. The largest cluster ($n=70$) comprised patients who did not currently meet criteria for depression, a cluster we named ‘Non-Depressed Patients’. More interestingly, two distinct phenotypes of depressive symptoms were identified in the 21 currently depressed patients with epilepsy (see Supplementary Material for dendrogram). We labelled the first, more common cluster ‘Cognitive Depression’ ($n=15$; 71%), as patients endorsed higher rates of cognitive depressive symptoms such as parasuicidal or suicidal thoughts, feelings of worthlessness, and delusions of guilt. They were also more likely to experience dysphoric mood compared to patients in the other cluster, and endorsed low rates of somatic symptoms and anhedonia (see Table 2). The base rate of Cognitive Depression in patients with focal epilepsy was 17%.

[Table 2 here]

We labelled the second, less common cluster ‘Somatic Depression’ (n=6; 29%), as these patients were significantly more likely than the Cognitive Depression group to feel anhedonic, and to endorse higher rates of biological symptoms such as appetite change and sleep disturbance. They were also less likely to endorse cognitive symptoms ($P>0.050$; see Table 2). In the current study, the base rate of Somatic Depression in patients with chronic focal epilepsy was 7%. Both phenotypes endorsed similarly high rates of excessive fatigue and subjective cognitive difficulties ($P>0.050$).

In terms of clinical epilepsy features, individuals with the Cognitive phenotype were more likely than non-depressed patients to have a left lateralized seizure focus [$\chi^2_{(1)}=4.448$, $P=0.034$, $\phi=-0.240$; small-medium effect size]. Neither phenotype differed from non-depressed patients on any other epileptological variables, or else in anticonvulsant or psychotropic pharmacotherapy ($P>0.05$ for all comparisons; see Table 3). Between the two depression phenotypes, patients with the Somatic form had more seizures than the Cognitive phenotype (49 versus 13 per month on average), and greater variability in their seizure frequency. The Somatic phenotype, however, had a shorter duration of epilepsy than the Cognitive phenotype (13 vs. 18 years) with seizures more commonly emerging in adulthood (67% vs. 47%). The two phenotypes were comparable in terms of seizure localization and lateralization.

[Table 3 here]

Cognitive profiles of the phenotypes of depression

The Cognitive phenotype of depression was characterized by poor memory function (see Supplementary Table A and Figure 2). Relative to healthy controls, patients with Cognitive Depression exhibited significantly reduced semantic and episodic autobiographic memory

across all life periods, including significantly worse overall semantic and episodic recollection. They also showed significantly reduced delayed recall across auditory-verbal ($P=0.032$) and visual domains ($P=0.002$) on the WMS-IV subtests, in the context of intact immediate learning ($P>0.050$). Patients with Somatic Depression showed a more muted and restricted profile of reduced memory, with poorer performances than controls on childhood episodic, early adulthood semantic, overall episodic, and delayed visual recall (see Supplementary Table B). FSIQ was comparable ($P>0.050$; Cognitive Depression= 98.710 ± 9.450 ; Somatic Depression= 97.750 ± 9.179).

Odds ratio analysis suggested that compared to patients with Somatic Depression, depressed patients with the Cognitive phenotype were (i) 3.640 times more likely to have a semantic autobiographic memory deficit (i.e., AMI subscale score <50 ; 95%CI= 0.162-81.705), (ii) 2.286 times more likely to have an episodic autobiographic memory deficit (i.e., AMI subscale score <16 ; 95%CI=0.316-16.512), (iii) 2.250 times more likely to have significantly impaired immediate verbal learning (i.e., WMS-IV score ≤ 8 ; 95%CI= 0.252-20.131), (iv) 6.000 times more likely to have significantly impaired delayed verbal recall (95%CI= 0.478-75.347), (v) 5.133 times more likely to have significantly impaired immediate visual learning (95%CI= 0.218-121.108), and (vi) 6.000 times more likely to have significantly impaired delayed visual recall (95%CI= 0.478-75.347).

[Figure 2 about here]

Psychosocial and demographic features of the phenotypes of depression

In addition to their distinct cognitive profiles, the Cognitive and Somatic phenotypes had specific demographic, clinical, and psychological features (see Figure 3). Demographically, inspection of group trends suggested that depressed patients with the Somatic phenotype were more likely to be female (83%) than those with the Cognitive phenotype (47%; see Table 3).

The two phenotypes were otherwise comparable in terms of age and relationship status ($P > 0.05$ for both comparisons).

[Figure 3 goes here]

Psychologically, inspection of group trends suggested that the two phenotypes reported similar level of depressive symptoms on the NDDI-E. However individuals with the Somatic phenotype reported lower levels of family satisfaction than patients with the Cognitive phenotype, and endorsed higher symptoms of anxiety. In contrast, patients with the Cognitive phenotype reported slightly lower epilepsy-related quality of life (See Supplementary Table A). Only five patients (33%) with Cognitive Depression were being actively treated with psychotropic medication, however their symptoms were better recognized than the Somatic Depression phenotype, none of whom were being treated. This is broadly consistent with a recent study showing that only 29.7% of depressed patients with epilepsy were receiving psychological or psychotropic treatment. {22}

Discussion

We have discovered two clinically-distinct, symptom-based subtypes of depression in epilepsy. The first phenotype, Cognitive Depression, was more frequent and characterized by cognitive symptoms of depression, dysphoria, and prominent memory deficits. The second, Somatic Depression, was typified by vegetative features, anhedonia, elevated anxiety, female gender, onset of frequent seizures as an adult, and unsatisfactory family dynamics. Subjective cognitive difficulties and excessive fatigue were common to both phenotypes.

Cognitive and Somatic phenotypes of depression in other populations

This delineation of Cognitive and Somatic phenotypes supports the observation that depression in epilepsy is not a homogenous condition with a canonical presentation. {9}

Symptom clusters with predominantly somatic or cognitive features are also found in

psychiatric outpatients, community samples, and medical cohorts with coronary disease. {23-27} The ubiquity of the somatic and cognitive phenotypes illustrates that while the clinical presentation of depression is heterogeneous it is not random. Unique to this cohort of focal epilepsy, however, is the finding that the Somatic phenotype was less common. This is the inverse to what is seen in psychiatric populations {23-24} and may contribute to the low rate of recognition and under-diagnosis of depression in epilepsy. Given the higher frequency of the Cognitive phenotype (base rate of 17%) it could be argued that the aetiology of depression in epilepsy is more strongly linked to dysfunction in distinct neurocognitive networks than is typical of primary depression. Supporting this, there is a predominance of non-somatic depressive symptoms in post-stroke patients, {28} potentially pointing to common mechanisms underlying depression across neurological diseases that can selectively impact large-scale cognitive brain networks

Clinical implications

Despite increasing recognition of the significant impact of depression in epilepsy, the paucity of currently depressed patients receiving medical treatment (here only 33% and in other studies ~30% {22}) indicates that its management requires a shift in thinking amongst clinicians. Recognition of symptom subtypes constitutes such a shift that might improve diagnosis and treatment. For instance, the Somatic phenotype is characterized by symptoms that overlap with the side-effects of seizures and antiepileptic drug use, potentially leading to an incorrect attribution of depressive symptoms such as sleep disturbance and weight gain to medical effects. Recognition that the features of depression in epilepsy may mimic the cognitive or vegetative correlates of seizures and antiepileptic medications could serve as a prompt for more detailed questioning around the emergence of cardinal diagnostic symptoms such as anhedonia and dysphoria.

The ubiquity of subjective memory complaints across the two phenotypes of depression may also hold immediate clinical utility. Rather than indexing objective cognitive ability, this characteristic feature may be better viewed as a sensitive marker of mood disturbance in epilepsy. This is commensurate with strong evidence that bitter memory complaints offered by people with epilepsy commonly reflect depression and anxiety, with formal neuropsychological assessment able to help differentiate between psychological and neurocognitive underpinnings and inform treatment decisions. {29-30} Moreover, lack of a proconvulsant effect of newer generation antidepressant medications should reassure clinicians of their safety for use in people with epilepsy. {31}

Correct classification of psychopathology remains a key goal, so that clinical features that reliably cluster together can be used to precisely predict the prognosis and treatment response of individuals. {23,32} In other populations, different phenotypes of depression may be at risk of different long-term health outcomes. In particular, somatic forms are considered cardiotoxic {25-27} and have been strongly linked to poor outcome after psychotropic treatment (N=811), {33} suggesting that Somatic Depression may require more aggressive treatment. A priority for future investigation should be replication of these phenotypes in other populations with epilepsy (e.g., community-based) as well as exploration of the negative health outcomes associated with each of the phenotypes of depression in epilepsy. Also important is whether appropriate and timely treatment of depression can be protective against cognitive decline or worsening seizures.

Conclusions

Critical to treatment of patients with depression and epilepsy is the accurate and early diagnosis of the comorbidity. The significance of the current study is the delineation of distinct phenotypes that are seen in other populations, including the unique finding to this cohort that the Somatic phenotype was less common. In the immediate future, we hope that

this typology will improve the recognition and management of depression in the busy neurology clinic. Looking forward, it is anticipated that meaningful phenotypes will provide clearer insights into the pathogenesis of depression in epilepsy and ultimately, guide the development of individually-tailored treatments.

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Figure Legends

Figure 1. Patient scores on cognitive and psychological measures converted into z-scores using healthy controls (n=77) as a baseline of normal task performance i.e., z-score = 0 ± 1 . Scores below zero represent impairments relative to controls, meaning that in the current study patients performed worse across all measures of memory and mood functioning. Error bars represent the standard error from the mean (SEM).

*= $P < 0.050$, **= $P < 0.010$, *** $P < 0.001$

Figure 2. Reduced neuropsychological functioning of the two depression phenotypes relative to a baseline of normal task performance provided by the control group (z score = 0 ± 1). Patients with the Cognitive phenotype perform worse than those with the Somatic phenotype across the majority of memory measures. Patients with the Somatic phenotype endorsed increased symptoms of anxiety.

Figure 3. Symptom profiles of the two phenotypes of depression in epilepsy, together with their psychosocial and cognitive correlates and putative underlying networks
AMN = autobiographic memory network; AN = affective network; CCN = cognitive control network

Supplementary Figure A: Dendrogram produced by hierarchical cluster analysis of the nine DSM-IV symptoms of depression using Ward Linkage, showing a clear three-cluster solution. The topmost cluster comprises non-depressed patients (cases 22-91), while the middle of the three clusters represents Somatic Depression (cases 16-21), and the bottom cluster represents Cognitive Depression (cases 1-15).

Table 1. Demographic and clinical profile of the sample (N=168)

	Epilepsy Patients (n=91)	Healthy Controls (n=77)
Age (years), $M \pm SD$	40.850 \pm 12.602	45.550 \pm 15.749
<i>Range</i>	20-69	21-69
Sex Female (%)	53 (58%)	48 (62%)
Education (years), $M \pm SD$	13.571 \pm 3.263	13.974 \pm 3.259
<i>Range</i>	5-24	9-21
Full-Scale IQ, $M \pm SD$	101.850 \pm 11.327 ^a	106.880 \pm 12.031 ^{b*}
<i>Range</i>	72-132	71-132
Age of seizure onset (years), $M \pm SD$	22.078 \pm 13.520	
<i>Range</i>	1.5 – 63	
Duration of epilepsy (years), $M \pm SD$	19.150 \pm 12.859	
<i>Range</i>	2 - 52	
Monthly average seizure frequency, $M \pm SD$	22.680 \pm 52.166	
<i>Range</i>	1 - 400	
$\leq 1/\text{month}$	21 (23%)	
Fortnightly (2-3/month)	14 (15%)	
Weekly (4-15 month)	36 (40%)	
More days than not ($\geq 16/\text{month}$)	20 (22%)	
Side of epilepsy focus		
Left	38 (42%)	
Right	44 (48%)	

Bilateral/Unclear	9 (10%)
Lobar focus,	
Temporal	68 (75%)
Frontal	10 (11%)
Parietal	6 (7%)
Other ^d	7 (8%)
Lesion positive (%)	58 (64%)
Antiepileptic drug polytherapy (%)	70 (77%)
Number of antiepileptic drugs, $M \pm SD$	2.24 \pm .993
<i>Range</i>	1 - 6

^a= four cases of missing data; ^b= eight cases of missing data; ^c= two cases of missing data; ^d= “Other” comprises four cases with foci localised to the posterior quadrant, and three cases with anterior quadrant foci

*= $P < 0.050$

Table 2. Two phenotypes of depression in epilepsy

DSM-IV Symptoms of Depression		Depression Subtype		Sig.	X ²	Effect Size (Φ) ^a
		Cognitive <i>n</i> = 15	Somatic <i>n</i> = 6			
Affective Symptoms	Dysphoria	93%	50%	^	5.219	0.499
	Anhedonia	13%	83%	**	9.450	0.671
Somatic Symptoms	Appetite Changes	27%	100%	**	9.240	0.663
	Sleep Changes	13%	83%	**	9.450	0.671
	Psychomotor Agitation	13%	33%		1.112	0.230
	Fatigue	60%	67%		0.081	0.062
Cognitive Symptoms	Worthlessness & Guilt	93%	50%	^	5.219	0.499
	Subjective Cognitive Difficulties	87%	100%		0.884	0.205
	Suicidality	67%	33%		0.304	0.304

^P = 0.053 (trend); **P < 0.010; X² degrees of freedom = 1

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; Sig.= significance level

^a= measure of effect size where 0.1 is considered a small effect, 0.3 a medium effect, and 0.5 a large effect.

The defining symptomatic features of each phenotype are highlighted in grey